Phase II, open-label, single arm, multicenter study of encorafenib, binimetinib plus cetuximab in subjects with previously untreated BRAF V600E - mutant Metastatic Colorectal Cancer

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Primary:- To evaluate the antitumor activity of the combination of encorafenib, binimetinib and cetuximab by assessing the confirmed overall response rate (cORR) by local radiologist/investigator assessment in adult subjects with previously…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50375

Source
ToetsingOnline

Brief title
W00090 GE 2 01
ANCHOR CRC Study

Condition

- Other condition

Synonym
Metatstatic Colorectal Cancer with a mutation of the BRAF V600E gene

Health condition

BRAF V600E -mutant Metastatic Colorectal Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pierre Fabre
Source(s) of monetary or material Support: by Sponsor; Pierre Fabre Médicament

Intervention

Keyword: BRAFV600E -mutatation, Metastatic Colorectal Cancer, Phase II, untreated

Outcome measures

Primary outcome

cORR as assessed by local radiologist/investigator review as per Response

Evaluation Criteria in Solid Tumors (RECIST 1.1).

Secondary outcome

- cORR as assessed by central radiologist review as per RECIST 1.1.

- ORR (for confirmed and unconfirmed responses) as per local

radiologist/investigator and central assessment.

- DOR assessed based on local radiologist/investigator and central review.

- TTR assessed based on local radiologist/investigator and central review.

- PFS assessed based on local radiologist/investigator and central review.

- OS.

- Type and severity of adverse events (AEs) and serious adverse events (SAEs),

changes in hematology and chemistry values, physical examinations, vital signs,

electrocardiogram (ECGs) and echocardiogram (ECHO)/ multi-gated acquisition

(MUGA) scans and ophthalmological examinations graded according to the National

Cancer Institute Common Terminology Criteria for Adverse Events v4.03

(NCI-CTCAE v4.03).

- Change from baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer subjects (QLQ-C30), EuroQol-5D-5L (EQ-5D-5L), and Patient Global Impression of Change (PGIC).

- Resource utilization focused on hospitalizations occurring during the study treatment phase.

- Plasma concentrations of encorafenib, binimetinib and the active metabolite of binimetinib (AR00426032) and serum concentration of cetuximab.

Study description

Background summary

BRAF mutations, which lead to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signaling resulting in increased cell proliferation and survival occur in approximately 10% (range, 5*22%) of the unselected colorectal cancer (CRC) population with lower prevalence in more advanced subject populations.

The presence of a BRAFV600E mutation is considered a marker of poor prognosis in subjects with mCRC with a median survival of approximately 12 to 14 months in the first line for the metastatic setting compared to 21 to 25 months for subjects with BRAF wild-type (BRAFwt) tumors.

The combination of binimetinib, encorafenib, and cetuximab was tested in a BRAFV600E mutant human colorectal xenograft model. The average reduction in tumor volume across all animals was better in the group that received the triplet compared to the group that received encorafenib and cetuximab.

Consistent with nonclinical data in human colorectal cancer cell models, BRAF+MEK+EGFR inhibitors result in greater activity than a dual combination BRAF+EGFR of inhibitors in subjects with BRAFV600E mCRC.

There is a large ongoing multicenter randomized phase III study (NCT02928224), the
BEACON CRC study, evaluating binimetinib + encorafenib + cetuximab vs encorafenib + cetuximab compared with Investigator*s choice of irinotecan + cetuximab or FOLFIRI + cetuximab in subjects with BRAFV600E mutant mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. A

total of 30 subjects were treated in the safety lead-in (SLI), all of whom received binimetinib (45 mg twice day (BID)) + encorafenib (300 mg once daily (QD)) + cetuximab (400 mg/m2 initial dose then 250 mg/m2 once weekly (QW)). Among the 29 subjects with BRAFV600E mutant tumors (one patient had a BRAF non-V600E mutant tumor) the confirmed overall response rate (cORR) was 48% (14/29 patients) and was 62% in patients with one previous line of therapy (10/16 patients) including 8 partial responses (PR) and 2 complete responses (CR); and in those with two prior lines of therapy the cORR was 31%, (4/13) including 3 PR and 1 CR. Preliminary estimate of median progression*free survival (PFS) is 8.0 months (95% confidence interval (CI), 5.6*8.5 months), with 7 of 29 patients (24%) still in follow-up and progression-free at the cut off date. PFS was similar between patients who had 1 vs 2 previous regimens (median, 95% CI, 7.6 [4.0*8.3] vs 8.1 [4.1*10.8] months) (Van Cutsem E et al, 2018) The confirmed ORR of 48% and median PFS of 8.0 months with the triplet combination of binimetinib + encorafenib+cetuximab exceeds historical standard-ofcare and exceeds the ORR of 22% in a phase II trial of the doublet of encorafenib + cetuximab (Tabernero et al. 2016).
The encouraging preliminary efficacy results observed in the SLI part of the BEACON
CRC study are consistent with the preclinical data and together justify the evaluation of this triple combination in the first-line setting of this population, which represents a high-unmet medical need.

Study objective

Primary:
- To evaluate the antitumor activity of the combination of encorafenib, binimetinib and cetuximab by assessing the confirmed overall response rate (cORR) by local radiologist/investigator assessment in adult subjects with previously untreated BRAF V600E-mutant (BRAFV600E) metastatic colorectal cancer (mCRC).
Secondary:
- To evaluate the cORR by central radiologist assessment.
- To evaluate the ORR (for confirmed and unconfirmed responses) by local radiologist/investigator and central assessment.
- To assess the effect of the combination of encorafenib, binimetinib and cetuximab on the duration of response (DOR).
- To assess the effect of the combination of encorafenib, binimetinib and cetuximab on other time-related efficacy parameters: time to response (TTR), progression-free survival (PFS) and overall survival (OS).
- To characterize the safety and tolerability of the combination of encorafenib, binimetinib and cetuximab.
- To assess the effect on quality of life (QoL).
- To explore health care resource utilization.
- To describe the pharmacokinetics (PK) of encorafenib, binimetinib, a metabolite of binimetinib (AR00426032) and cetuximab.

Study design

This is a multinational, multicenter, open-label, single-arm phase II study to evaluate the combination of encorafenib, binimetinib and cetuximab in subjects with BRAFV600E mutant mCRC who have not received any prior systemic therapy for metastatic disease.
Subjects will be eligible for the study based on identification of a BRAFV600E mutation in the tumor tissue as determined by local laboratory result obtained at any time prior to Screening. Only polymerase chain reaction (PCR) and next generation sequencing (NGS)-based results will be acceptable. The BRAF mutation status must be confirmed by central laboratory no later than 30 days after the first dose of study treatment. In cases where there is discordance between the local assay and central laboratory results, or if the central laboratory is not able to confirm presence of a BRAFV600E mutation due to inadequate or poor sample condition within 30 days of initiating study therapy, subjects may only continue treatment if there is no clinical indication of deterioration or disease progression and the Investigator determines that the subject is deriving benefit. In such instances, subjects must be informed that the BRAF mutation status is unconfirmed and must sign a separate informed consent form (ICF) that includes this information and describes alternative treatment options.
Treatment phase
The study will include two stages according to a two-stage design.
Stage 1: In the first stage, 40 subjects will be treated. In case of discordance in the results between the local assay and the central laboratory (potential falsepositive local result), or lack of BRAFV600E confirmation, subject will be replaced for the primary analysis of the futility analysis. If there are 11 or fewer confirmed responses (CR or PR) in the 40 treated subjects with a centrally confirmed BRAFV600E mutation, the study will be stopped. Otherwise, additional subjects will enter stage 2 . Stage 2 may be initiated as soon as 40 subjects with a centrally confirmed BRAFV600E mutation are treated and confirmed responses are observed in at least 12 subjects.
Stage 2: 50 additional subjects will be treated, for a total of 90 subjects with a centrally confirmed BRAFV600E mutation. In case of discordance in the results between the local assay and the central laboratory (potential false-positive local result), or lack of BRAFV600E confirmation, subject enrolled in the stage two of the trial will be replaced for the primary analysis.
If at any time during the study, either in stage 1 or in stage 2, there is discordance or impossibility to confirm the BRAFV600E mutation in 3 subjects, all subsequent subjects will be required to have BRAFV600E determined by the central laboratory prior to study treatment assignment.
For the statistical design, please refer to the statistical section of the protocol. Treatment will be administered in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy or death. In special circumstances, continuation

of treatment after disease progression may be allowed. After treatment is discontinued, subjects will be followed for survival until 1 year after the start of study treatment of the last subject enrolled.

Intervention

Encorafenib: 300 mg orally per os (oral capsule 4X 75 mg) once daily.
Binimetinib: 45 mg orally per os (oral tablet 3X 15 mg) twice daily.
Cetuximab: 400 mg/m2 intravenous (IV) at Cycle 1 day 1 then 250 mg/m2 IV every week (QW) for the first 28 weeks. Then, 500mg/m2 IV every two weeks (Q2W) from week 29 (Cycle 8 day 1).
If there is a dose modification prior to switching to the biweekly schedule, the total dose per cycle should be maintained (i.e. 200mg/m2 QW may be changed to a 400mg/m2 Q2W).
Cycle duration: 28 days.

Study burden and risks

The data obtained from previous studies suggest that the triple combination of encorafenib/binimetinib/ cetuximab may be effective to treat patients with colorectal cancer.
There is a large international study (called BEACON study) evaluating the same treatment combination as the one being administered in this study for patients with more advanced disease. The first results of the BEACON study show that this treatment combination may be effective in patients with advanced colorectal cancer with this mutation (BRAF V600E). However, the study is still ongoing and final results have not been reported yet, therefore, no conclusion can be made at this point.
This is the first time this triple combination will be administered to patients with colorectal cancer who have not received any previous treatment for their metastatic disease.

Patients will have biopsies that could potentially cause pain, swelling, bleeding and/or infection at the site where the biopsy needle penetrates. There is also the possibility that having this procedure may shift some cells from the tumor into the surrounding tissues (tissues that come into contact with the biopsy needle).
-The imaging examinations (CT-scan, multi-gated acquisition and MRI) will expose patients to limited doses of radiation and the risk of an allergic reaction to the contrast agents used.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provide a signed and dated informed consent document.
2. Male or female * 18 years of age at time of informed consent.
3. Histologically or cytologically confirmed CRC that is metastatic and unresectable at time of study entry (i.e. not suitable for complete surgical resection at screening).
4. Presence of BRAFV600E mutation in tumor tissue previously determined by a local assay at any time prior to screening.
Notes:
a. Only PCR and NGS-based local assays results will be acceptable.
b.If at any time there is lack of confirmation of the BRAFV600E mutation in a total of 6 subjects (* 6% of the total targeted 90 treated subjects) or discordance between the local assay and the central laboratory in 3 subjects (* 3% of the total targeted 90 treated subjects), all subsequent subjects will be required to have BRAFV600E determined by the central lab prior to study treatment assignment.
c. Central testing cannot be repeated to resolve discordances with a local

result once the central laboratory delivers a definitive result (positive or negative).
d. If the result from the central laboratory is indeterminate or the sample is deemed inadequate for testing, additional samples may be submitted (archival material only).
e. If more than 1 discordant result from any local laboratory lead to subject enrollment, subsequent results from this local laboratory will not be accepted for further subject enrollment.
5. Eligible to receive cetuximab per locally approved label with regards to tumor RAS status
e.g.: In agreement with EU label, evidence of wild type RAS (KRAS and NRAS) status in EU countries
6. Able to provide a sufficient amount of representative tumor specimen (primary or metastatic, archival or newly obtained) for testing of BRAF and RAS mutation status(FFPE tumor tissue block or a minimum of 10 slides, optimally up to 15 slides)
7. Evidence of measurable disease, as per RECIST 1.1.
Note: Lesions in areas of prior radiotherapy or other loco-regional therapies are considered measurable only if progression has been documented in the region following therapy.
8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
9. Adequate bone marrow function at screening and baseline:
i. Absolute neutrophil count (ANC) * 1.5 x 1 000 000 000 /L.
ii. Platelets * 100 x 1 000 000 000/L
iii. Hemoglobin * 9.0 g/dL.
Blood transfusions are allowed provided that the subject has not received more than 2 units of red blood cells in the 4 weeks prior to achieve the minimum required hemoglobin level.
10. Adequate renal function at screening and baseline:
i. Serum creatinine * 1.5x upper limit of normal (ULN).
ii. Calculated creatinine clearance (CrCl)* 50 mL/min by Cockroft-Gault formula.
11. Adequate electrolytes at screening and baseline, defined as serum potassium and magnesium levels within institutional normal limits.
Replacement treatment to achieve adequate electrolytes will be allowed
12. Adequate hepatic function at screening and baseline:
i. Serum total bilirubin * 1.5 x ULN and < 2 mg/dL. Total bilirubin > 1.5 x ULN is allowed if direct (conjugated) bilirubin is * 1.5 x ULN.
ii. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) * 2.5 x ULN, or * 5 x ULN in the presence of liver metastases.
13. Adequate cardiac function at screening:
i. Left ventricular ejection fraction (LVEF) * 50% as determined by MUGA scan or ECHO.
ii. Mean triplicate QT interval corrected for heart rate according to Fridericia*s formula (QTcF) value * 480 msec.
14. Subject able to take oral medications.
15. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

16. Female subjects are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks, or must agree to take appropriate precautions to avoid pregnancy.
(a) Precautions to avoid pregnancy must be conducted from screening through 6 months after the last dose of cetuximab or through 30 days after the last dose of encorafenib or binimetinib, whichever is later if of childbearing potential.
(b) Permitted methods of contraception as provided (in Section 5.3.1) should be communicated to the subjects and their understanding confirmed. For all females, the pregnancy test must be negative at screening and baseline.
17. Male subject must agree to take appropriate precautions to avoid fathering a child
(a) from screening through 6 months after the last dose of cetuximab or through 90 days after the last dose of encorafenib or binimetinib, whichever is later.
(b) permitted methods of contraception as provided (in Section 5.3.1) should be communicated to the subjects and their understanding confirmed.
18. Patients under guardianship or partial guardianship will be eligible unless prohibited by local laws or by local/central ethic committees.
Note: where allowed, all procedures prescribed by law must be followed.
19. Affiliated to a social security system, or is a beneficiary (if applicable in the national regulation).

Exclusion criteria

1. Prior systemic therapy for metastatic disease.
Note: previous adjuvant/neoadjuvant therapy is allowed provided that 1) the interval from the end of chemotherapy to relapse is >6 months 2) in the case of neoadjuvant therapy, complete surgical resection was achieved and the interval from the end of chemotherapy to relapse is >12 months. Prior locoregional radiotherapy is allowed.
2. Prior treatment with any RAF inhibitor, MEK inhibitor, cetuximab or other anti- EGFR treatment.
3. Symptomatic brain metastasis.
Note: subjects previously treated or untreated for these conditions who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for * 4 weeks with imaging
4. Leptomeningeal disease.
5. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity syndrome or hypercoagulability syndrome.
6. Use of any herbal medications/supplements or any medications or foods that are moderate or strong inhibitors or inducers of CYP3A4/5 * 1 week prior to the start of treatment.
Note: However, subjects who either discontinue moderate or strong inhibitors or inducers of CYP3A4/5 or switch to another medication at least 7 days prior to starting study treatment are eligible.

7. Known history of acute or chronic pancreatitis within 6 months prior to the start of the treatment.
8. History of chronic inflammatory bowel disease or Crohn*s disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) * 12 months prior to first dose.
9. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
i. History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft, coronary angioplasty or stenting) * 6 months prior to start of study treatment.
ii. Symptomatic congestive heart failure (Grade 2 or higher), history or current evidence of clinically significant arrhythmia and/or conduction abnormality * 6 months prior to start of study treatment, except atrial fibrillation and paroxysmal supraventricular tachycardia.
10. Uncontrolled hypertension defined as persistent elevation of systolic blood pressure * 150 mmHg or diastolic blood pressure * 100 mmHg despite optimal therapy.
11. Impaired hepatic function, defined as Child-Pugh class B or C.
12. No more applicable from protocol v6.
13. Impaired gastrointestinal function or disease which may significantly alter the absorption of encorafenib or binimetinib or recent changes in bowel function suggesting current or impending bowel obstruction.
14. Previous or concurrent malignancy within 5 years of study entry or other noninvasive or indolent malignancy without Sponsor approval except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix.
15. History of thromboembolic or cerebrovascular events * 6 months prior to starting study treatment including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli.
16. Concurrent neuromuscular disorder that is associated with the potential of elevated Creatine Kinase e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy.
17. Residual CTCAE * Grade 2 toxicity from any prior anticancer therapy, with the exception of Grade 2 alopecia or Grade 2 neuropathy.
18. Known history of human immunodeficiency virus infection.
19. Active hepatitis B or hepatitis C infection.
20. Known contraindication to receive cetuximab at the planned doses.
21. Subjects who have any medical condition that would, in the Investigator*s judgment, prevent the subject*s participation in the clinical study due to safety concerns or compliance with study procedures.
22. Any medical or psychiatric condition or laboratory abnormality that may increase the risk with study participation or study drug administration or that may interfere with the interpretation of study.
23. Pregnancy, confirmed by a positive human chorionic gonadotropin laboratory test result, or breastfeeding.
24. Is a family member of the Investigator or any associate, colleague, or employee assisting in the conduct of the study

25. Is in a position likely to represent a conflict of interest.
26. Participation in a clinical study with administration of an investigational product within 4 weeks before the first dose of study treatment.
27. Is mentally unable to understand the nature, objectives and possible consequences of the trial; or he/she refuses to its constraints.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-12-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Braftovi
Generic name:	encorafenib
Product type:	Medicine
Brand name:	Erbitux
Generic name:	Cetuximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Mektovi
Generic name:	binimetinib

Ethics review

Approved WMO Date:	13-09-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-000271-32-NL
CCMO	NL64952.018.18